SnapShot: Pathogenesis of Parkinson's Disease

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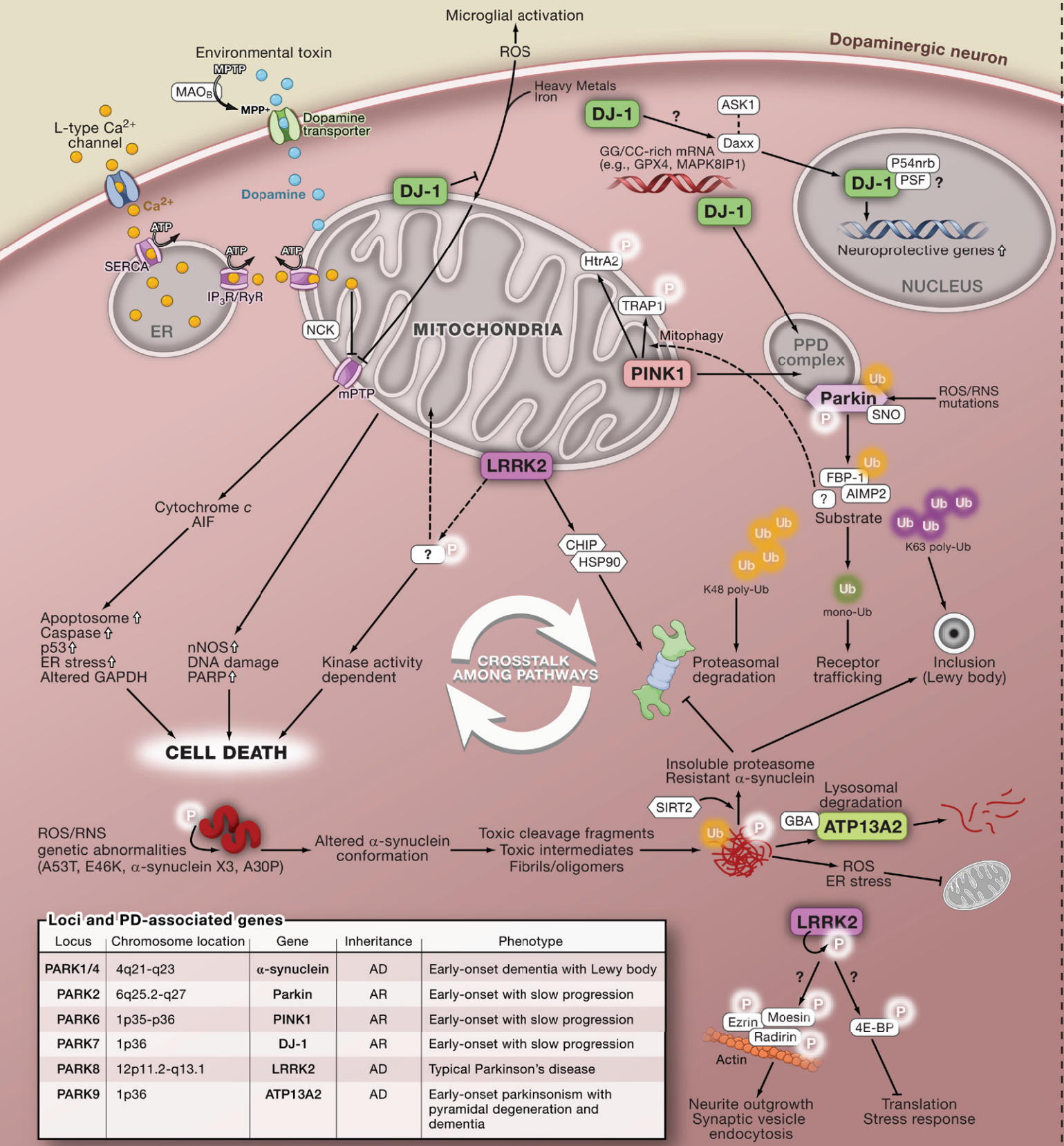

Loci and PD-associated genes

Locus	Chromosome location	Gene	Inheritance	Phenotype
PARK1/4	4q21-q23	α-synuclein	AD	Early-onset dementia with Lewy body
PARK2	6q25.2-q27	Parkin	AR	Early-onset with slow progression
PARK6	1p35-p36	PINK1	AR	Early-onset with slow progression
PARK7	1p36	DJ-1	AR	Early-onset with slow progression
PARK8	12p11.2-q13.1	LRRK2	AD	Typical Parkinson's disease
PARK9	1p36	ATP13A2	AD	Early-onset parkinsonism with pyramidal degeneration and dementia

See online version for legend and references.

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Cell

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Parkinson's disease (PD) is the most common movement disorder characterized by death of dopaminergic neurons in the substantia nigra pars compacta. Sophisticated genetic analysis has revealed several PD-associated genes including those encoding α-synuclein, parkin, PINK1, DJ-1, LRRK2, and ATP13A2 (see table). Diverse environmental factors in conjunction with genetic risk factors lead to PD pathogenesis, although the exact mechanisms are still under investigation. This SnapShot summarizes the roles that proteins encoded by PD-associated genes play in both common and divergent mechanisms of PD pathogenesis.

Death of Dopaminergic Neurons

Unlike most other brain neurons, the dopaminergic neurons of the substantia nigra use L-type Ca^{2+} channels (containing a distinctive Cav 1.3 pore-forming subunit, Cacna1d) for pace making, resulting in increased ATP consumption and Ca^{2+} influx. Ca^{2+} enters the endoplasmic reticulum (ER) via a high-affinity smooth ER Ca^{2+} (SERCA) pump. Ca^{2+} flows back into the cytoplasm through inositol trisphosphate receptors (IP_3R) and ryanodine receptors (RyR) forming a high-concentration Ca^{2+} zone near mitochondria. Mitochondria in dopaminergic neurons take up Ca^{2+} via the Ca^{2+} uniporter, whereas mitochondrial Ca^{2+} efflux is mediated by the Na^+/Ca^{2+} exchanger (NCX). Mitochondria are a key target in PD and impaired mitochondria contribute to death of dopaminergic neurons. Due to their unique Cav 1.3 calcium channels, dopaminergic neurons are more vulnerable to environmental toxins, such as 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP). MPTP selectively kills dopaminergic neurons by blocking the activity of mitochondrial complex I and has been used to create animal models of PD. Once monoamine oxidase B (MAOB) metabolizes MPTP into 1-methyl-4-phenyl-pyridium (MPP^+), MPP^+ is transported and concentrated in mitochondria by the dopamine transporter. This leads to inhibition of mitochondrial complex I, eventual depolarization of the mitochondrial membrane, and opening of the mitochondrial permeability transition pore (mPTP). This results in release of mitochondrial cell death effectors such as cytochrome *c* and apoptosis-inducing factor (AIF). Ultimately death of the dopaminergic neuron ensues through various cell death cascades including caspase-dependent and caspase-independent pathways, ER stress, neuronal nitric oxide synthase (nNOS) activation, DNA damage, poly(ADP-ribose) polymerase (PARP) activation, and GAPDH modification. Microglial activation also contributes to the demise of dopaminergic neurons.

PD Genes and Molecular Pathogenesis

Autosomal-Dominant

α-Synuclein: Even though the physiological function of α-synuclein is still unclear, numerous studies indicate its association with membranes, synaptic vesicle recycling, dopamine neurotransmission, and lipid interactions. This protein is the major structural component of Lewy bodies, which are the pathological hallmark of PD. Identification of genetic abnormalities in the *α-synuclein* gene have implicated the protein encoded by this gene in the pathophysiology of PD. Native unfolded or altered α-synuclein monomers with genetic modifications (A53T, E46K, A30P) form toxic intermediates such as oligomers and fibrils, which eventually form Lewy bodies. Triplication of the *α-synuclein* gene (X3) can also lead to PD due to the simple increase in the steady-state level of wild-type α-synuclein. In sporadic PD, reactive oxygen species (ROS), reactive nitrogen species (RNS), and aging play a role in the aggregation of α-synuclein. ROS/RNS production, disruption of macroautophagy, mitochondrial dysfunction, and proteasome inhibition can also be triggered by mutant or aggregated α-synuclein. The histone deacetylase, Sirtuin2 (SIRT2), may also contribute to PD pathogenesis.

LRRK2: LRRK2 consists of diverse domains, including a leucine-rich repeat, a Roc GTPase domain, a COR (C-terminal of Ras) domain, a kinase domain, and a WD40-repeat. LRRK2 is localized in the cytoplasm and is associated with membranous structures including mitochondria, the ER, and synaptic vesicles. Familial mutants of LRRK2 result in a gain of function and neuronal toxicity that is kinase dependent and regulated by the chaperones CHIP and HSP90. These chaperones control LRRK2 levels through the ubiquitin-proteasome system. Moesin is a putative LRRK2 substrate. Functional studies implicate LRRK2 in neurite outgrowth and the endocytosis of synaptic vesicles. 4E-BP is a putative LRRK2 substrate, suggesting that LRRK2 is involved in translation. Data suggest that LRRK2 may also regulate mitochondrial function. Disease-causing mutations in human LRRK2 consistently cause α-synuclein pathology.

Autosomal-Recessive

PINK1: Little is known about the function of PINK1, other than that it is thought to be a mitochondrial kinase that acts upstream of parkin in the PD pathogenesis cascade. Disease-causing mutations in PINK1 may lead to a loss of function. The mitochondrial chaperone, TRAP1, and the serine protease, HtrA2, are putative PINK1 substrates that play important roles in regulating mitochondrial function and mitochondrial-dependent cell death pathways. PINK1 may also physiologically regulate Ca^{2+} efflux from the mitochondria via NCK.

DJ-1: DJ-1 is a molecular chaperone with multiple functions. Disease-causing mutations in DJ-1 may lead to a loss of function. DJ-1 regulates ROS levels by acting as an atypical peroxiredoxin-like peroxidase and also modulates RNA metabolism and gene transcription. In addition, DJ-1 may bind to Daxx/apoptosis signal-regulating kinase1 (ASK1) and inhibit ASK1 activity and cell death. DJ-1 is also involved in a Parkin-PINK1-DJ-1 (PPD) complex that promotes the degradation of unfolded proteins.

Parkin: Mutations in the *parkin* gene and posttranslational modifications to the protein, such as phosphorylation or S-nitrosylation (SNO) by ROS/RNS, block parkin's ability to function as an E3 ubiquitin ligase. This leads to the accumulation of its substrates, including AIMP2, FBP-1, and others, which are somehow involved in mitochondrial dysfunction and neuronal toxicity. Parkin uses poly-K48 ubiquitin linkages to promote degradation of its substrates. Parkin also uses poly-K63 ubiquitin linkages or mono-ubiquitination to regulate intracellular signaling, receptor trafficking, and the formation of inclusions. Parkin acts downstream of PINK1 in genetic models and appears to play a role in the clearance of mitochondria by autophagy (mitophagy).

ATP13A2: ATP13A2 is a large lysosomal P-type ATPase. Although functional studies are at a very early stage, it is thought that ATP13A2 and the PD susceptibility gene encoding β-glucocerebrosidase (GBA) may be involved in the clearance of α-synuclein aggregates.

Abbreviations

AD, autosomal-dominant; AR, autosomal-recessive; 4E-BP, eukaryotic initiation factor 4E (eIF4E)-binding protein; PSF, pyrimidine tract-binding protein-associated splicing factor; p54nrb, p54 nuclear RNA-binding protein; GPX4, glutathione peroxidase 4; MAPK8IP1, mitogen-activated protein kinase 8-interacting protein 1; Ub, ubiquitin.

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